

Achilles' heel of drug-eluting stents as compared with bare-metal stents, before our study, there was little information about the short- and long-term comparative safety and efficacy of these devices for off-label indications. Our study has filled the short-term knowledge gap with data from 1 year of follow-up, and with the recent receipt of funding from the National Heart, Lung, and Blood Institute Dynamic Registry for continued follow-up of these patients, it is our goal to help fill the knowledge gap regarding the long-term safety and efficacy of these devices.

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1. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 2007;297:1992-2000.
2. Vermeersch P, Agostoni P, Verheye S, et al. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol* 2007;50:261-7.

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

TO THE EDITOR: Ekberg et al. (Dec. 20 issue)¹ report the results of the Efficacy Limiting Toxicity Elimination (ELITE)–Symphony trial, in which they evaluated reduced exposure to calcineurin inhibitors in patients undergoing renal transplantation. The authors' putative conclusion is that a quadruple immunosuppressive regimen of daclizumab, "low-dose" tacrolimus, mycophenolate mofetil, and corticosteroids should be considered the standard in renal transplantation. We have concerns, however, about the equipotency of the four immunosuppressive strategies used. The trough levels of sirolimus that were achieved in the calcineurin-inhibitor-free group have not been demonstrated to be clinically effective and are, in our view, probably too low to protect grafts from acute rejection early after transplantation. In addition, the use of mammalian target of rapamycin (mTOR) inhibitors such as sirolimus immediately after transplantation is well known to be associated with a variety of acute postsurgical complications — for example, wound healing problems — as seen in this study. Therefore, most clinicians and current study designs strongly favor the delayed introduction of mTOR inhibitors. The high rates of side effects and drug discontinuation seen in the calcineurin-inhibitor-free group may be due largely to an ill-timed early initiation of sirolimus after transplantation. With these study-design limitations, we believe that clinicians should use caution

when considering whether to abandon other potentially valuable immunosuppressive regimens on the basis of the conclusions from this study.

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1. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007;357:2562-75.

TO THE EDITOR: Some further issues need to be considered in interpreting the results of the study by Ekberg et al. It is well known that cyclosporine, but not tacrolimus, diminishes enterohepatic recirculation of the major mycophenolic acid metabolite, mycophenolic acid glucuronide, thereby resulting in a lower exposure to mycophenolic acid in the cyclosporine groups. Such a drug–drug interaction might explain some of the results of the present study.¹ Currently, protocols are under study that use a loading dose of mycophenolic acid, which may overcome the problem of early low exposure.

New-onset diabetes after transplantation is considered an important adverse effect after renal transplantation. Therefore, readers need to know how new-onset diabetes after transplantation was defined in the present trial. Was the definition

based on the American Diabetes Association–World Health Organization guidelines as suggested in 2003?²

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1. Hesselink DA, van Hest RM, Mathot RAA, et al. Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance-associated protein 2. *Am J Transplant* 2005;5:987-94.
2. Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 international consensus guidelines. *Transplantation* 2003;75:Suppl:SS3-SS24.

TO THE EDITOR: Ekberg et al. suggest that treatment with a combination of low-dose tacrolimus with daclizumab, mycophenolic acid, and corticosteroids is superior with regard to renal function, renal allograft survival, and acute rejection. However, the primary end point, the calculated glomerular filtration rate at month 12, depends heavily on the completeness of the data. Both the group that received standard-dose cyclosporine and the group that received low-dose sirolimus were at a disadvantage because of higher numbers of patients with missing values (37 and 38 patients in these two groups, respectively, vs. 25 and 24 in the low-dose cyclosporine and low-dose tacrolimus groups, respectively, with the missing value arbitrarily calculated as 10 ml per minute). Fourteen missing calculations of the glomerular filtration rate result in a mean glomerular filtration rate that is estimated to be 1.75 ml per minute lower for the whole group. Along these lines, when the measured glomerular filtration rate was used, differences between groups were much smaller. The authors should provide an explanation for this imbalance with regard to missing values. How would the calculated mean glomerular filtration rates be affected if imputed values and the last observation carried forward were not used for missing values?

What was the timing of the last observation carried forward in the different groups? What value was used for the glomerular filtration rate in patients who had graft loss, died, or both?

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Drs. Krämer and Banas report having participated in clinical trials sponsored by Astellas, Novartis, Roche, and Wyeth. Dr. Krämer reports receiving lecture fees from Astellas, Novartis, and Wyeth; being a member of advisory or safety boards for Astellas, Novartis, and Wyeth; and receiving research grants from Astellas and Novartis. No other potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: On the basis of the results of the ELITE–Symphony study, Ekberg et al. conclude that a regimen containing daclizumab, mycophenolate mofetil, corticosteroids, and low-dose tacrolimus may offer an advantage over other immunosuppressive regimens after renal transplantation. However, the design of the study did not include a regimen containing standard-dose tacrolimus without daclizumab induction, whereas such a triple regimen is currently the standard in many transplantation centers. Moreover, the additional drug costs of about \$6,500 (U.S.) incurred by the use of daclizumab are not discussed. Another strategy to reduce the adverse effects of calcineurin inhibitors is to discontinue their use in immunologically low-risk patients. Such an approach has been associated with favorable long-term results^{1,2} and is probably more cost-effective.

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1. Bakker RC, Hollander AA, Mallat MJ, Bruijn JA, Paul LC, de Fijter JW. Conversion from cyclosporine to azathioprine at three months reduces the incidence of chronic allograft nephropathy. *Kidney Int* 2003;64:1027-34.
2. Joss N, Rodger RS, McMillan MA, Junor BJ. Randomized study comparing cyclosporine with azathioprine one year after renal transplantation — 15-year outcome data. *Transplantation* 2007;83:582-7.

THE AUTHORS REPLY: The objective of the ELITE–Symphony study was to identify a regimen of low toxicity and high efficacy. The choice of trough levels was based on commonly used long-term maintenance levels that we used from the day of transplantation and that we hypothesized to be equipotent. The results indicate that they were

not — a concern raised by Guba and Jauch; the sirolimus-based regimen was less effective but also had the highest toxicity and the greatest number of premature withdrawals. We concur that sirolimus toxicity may be reduced if its use after transplantation is delayed.

Krüger and colleagues suggest that reduced exposure to mycophenolic acid in the cyclosporine group because of a drug–drug interaction may, in part, explain our results. We agree, but for two reasons we do not believe this is a major issue. First, although mycophenolic acid exposure is greater when mycophenolate mofetil is given in combination with sirolimus¹ or tacrolimus² than when it is administered with cyclosporine, the results for the sirolimus group were discordant with those for the tacrolimus group. Second, a larger proportion of patients in the tacrolimus and sirolimus groups received doses of mycophenolate mofetil that were lower than the specified dose (2 g per day) over the first 6-month period after transplantation, which would have reduced the difference in mycophenolic acid exposure between these groups and the cyclosporine groups. Regarding the comment about new-onset diabetes after transplantation, our study was designed in 2002, when there was no established consensus definition for this condition, and before publication of the American Diabetes Association–World Health Organization guidelines. New-onset diabetes after transplantation in the ELITE–Symphony study was defined as adverse-event reports that included the term “diabetes” or “hyperglycemia.” However, only a small fraction of patients became insulin-dependent.

We agree with Krämer and colleagues that the

calculated glomerular filtration rate can be influenced by the degree of completeness of the data. We conducted several sensitivity analyses for the mean glomerular filtration rate with different imputations and use of the last-observation-carried-forward method. These analyses yielded the same pattern of results as those reported in our article, thus confirming the robustness of the results.

Finally, van den Hoogen and Hilbrands suggest that our study should have included a triple regimen containing standard-dose tacrolimus without daclizumab induction. However, standard-dose cyclosporine was considered the benchmark when our study was designed. Regarding the comment about additional drug costs associated with daclizumab, health economics was not part of the scope of our article, nor were long-term changes in the maintenance treatment.

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1. Picard N, Prémaud A, Rousseau A, Le Meur Y, Marquet P. A comparison of the effect of ciclosporin and sirolimus on the pharmacokinetics of mycophenolate in renal transplant patients. *Br J Clin Pharmacol* 2006;62:477-84.

2. Zucker K, Rosen A, Tsaroucha A, et al. Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous in vitro findings. *Transpl Immunol* 1997;5:225-32.

Nasal CPAP for Very Preterm Infants

TO THE EDITOR: In the trial reported by Morley et al. (Feb. 14 issue),¹ a significant reduction in the use of surfactant in the group treated with early continuous positive airway pressure (CPAP) as compared with the intubation group (38% vs. 77%) was perhaps the most striking finding. In the CPAP group, the median time for intubation was 6.6 hours (interquartile range, 2.2 to 19.3), and we inferred from this that surfactant was probably given as a rescue treatment. Since the timing of surfactant therapy is likely to affect outcome measures,²

perhaps the advantages of early CPAP balanced out the advantages of early surfactant treatment in the intubation group. To address this question, a detailed comparison of the timing of surfactant treatment in both groups would be of interest.

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